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Real-world treatments and clinical outcomes in unfit AML patients receiving first-line treatment or best supportive care in Italy (CURRENT study)

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ABSTRACT

Real-world data on treatment patterns and outcomes of patients with acute myeloid leukemia unfit for intensive chemotherapy are lacking before the advent of precision medicine in this setting.

Herein, we present the Italian sub-analysis of the CURRENT study in AML patients unfit for first line intensive chemotherapy, evaluating patients' outcomes between 2015 and 2018.

Among 74 evaluable patients, 62 received systemic treatments (most used therapy was hypomethylating agents), while 12 best supportive care.

Key results include both efficacy and safety data, as well as HCRU and treatment patterns. In first-line therapy cohort median OS was 13.4 months vs. 2.7 months for BSC.

1. Introduction

Acute myeloid leukemia (AML) is a heterogeneous hematologic malignancy and, while rare, it is the most common acute leukemia and has the worst prognosis among all leukemia subtypes [1,2]. AML is more common in individuals over 55 years of age, and as such is more prevalent in the elderly [1]. Given the progressive aging of the general population, the burden for healthcare systems has steadily increased in recent years [3].

Prognosis of elderly AML patients greatly differs from that of younger patients, with a 5-year overall survival of about <25 % and <10 % among those 60–65 and ≥70 years old, respectively, compared to roughly 50 % among patients with an age < 50 years [1,2]. In routine management of patients with AML, particularly in the elderly, one of the first steps is to evaluate overall fitness status in terms of ability to tolerate intensive induction chemotherapy [4]. Compared to palliative therapy, either intensive chemotherapy or attenuated treatment with hypomethylating agents (HMA) have been associated with better outcomes.

Starting from early 2000s, HMAs have been shown to provide clinical benefit to older AML patients. Either azacytidine or decitabine have represented the only alternative to supportive care for unfit patients and have remained the only option available to them for years [5]. Notwithstanding, the outcome of AML patients who are not eligible for intensive chemotherapy still remains extremely poor [4].

Real-world data on treatment patterns and clinical outcomes of patients affected by AML and unfit for intensive chemotherapy are lacking especially considering the period when the therapeutic armamentarium

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was limited and no new molecules had yet been approved. Standard of care in AML is evolving, and considering the increasing incidence and rising costs of treatment, there is a need to understand the AML treatment strategies, the associated treatment outcomes, and the socio-economic impact.

CURRENT is a multi-country non-interventional, retrospective chart review aimed at evaluating the treatment pathways and outcomes, and health care resource utilization of AML patients unfit for intensive chemotherapy who received first-line non-intensive systemic treatment or best supportive care (BSC) in a real-world setting. Herein we present the final analysis of the CURRENT population enrolled in Italy.

2. Materials and methods

2.1. Study design

CURRENT was a non-interventional, retrospective chart review conducted across 22 countries; 7 centers were involved in Italy. Global results have been described elsewhere [6,7] as well as two countries specific sub-analyses coming from Canada and Japan [8,9]. Adult patients with newly diagnosed AML, both *de novo* or secondary, who were not candidates for intensive induction chemotherapy as defined by the treating physician between January 2015 and December 2018 were eligible for enrollment. Ineligibility for intensive induction therapy and treatment were defined based on the treating physician's assessment of fitness, age, Eastern Cooperative Oncology Group (ECOG) performance status, comorbidities, regional guidelines, institutional practice, or all the above. During the treatment period patients must have had ≥ 2 visits in addition to the initial event visit. Patients with an unconfirmed diagnosis, acute promyelocytic leukemia, or who received first-line treatment within a clinical trial were excluded.

The primary endpoint was overall survival (OS) from diagnosis; secondary endpoints included progression-free survival (PFS), time to treatment failure (TTF), response rates (defined as complete remission [CR], complete remission with incomplete hematologic recovery [CRi], and partial remission [PR]) according to the treating physician's assessment, measurable residual disease (MRD), and healthcare resource utilization (HCRU). TTF was defined as the time from start of systemic therapy including low intensity chemotherapy, targeted therapy or BSC until discontinuation of treatment for any reason including disease progression, death, toxicity, or the patient's / physician's choice.

Patients were followed-up until last recorded contact or death. Data collection was anonymized and did not enable patient identification; as such, written consent was not required for participation in the study. All ethics committees at the participating centers approved the study according to local regulations.

2.2. Statistical analysis

Globally the study had a target sample size of 1600 AML patients, 81 of whom in Italy, object of this analysis. The total sample size was considered sufficient to provide precise estimates, e.g. with $n = 1200$ (using normal approximation for binomial distribution) a width of a two-sided 95 % confidence interval (CI) within ±2.8 % was foreseen for proportion based estimates. For treatment subgroups ($n = 300$), geographic subgroups ($n = 200$), and combinations of these ($n = 50$), the widths were estimated to be ±5.7 %, ±6.9 %, and ±13.9 %. Results were analyzed for the overall population and for treatment subgroups (e.g. systemic therapy or BSC). For survival/time to event data (OS, PFS, TTF), the Kaplan–Meier method was used to estimate proportions and median times, and Kaplan Meier results are presented with two-sided 95 % CI.

3. Results

3.1. Patient characteristics and treatments

A total of 81 newly diagnosed AML patients were enrolled in Italy, of whom 74 were considered evaluable (Table 1; Supplemental Fig. 1). Of these, 62 had been treated with systemic therapies and 12 with BSC. Median age at diagnosis was 76.0 years in those receiving first-line systemic therapy and 79.0 years in those receiving BSC; 24 patients had secondary AML and 50 *de novo* AML. The two groups of patients were comparable in terms of molecular profile and cytogenetic risk, while patients who were candidates for BSC more often had an ECOG performance status score ≥ 2 (50% vs 33 %). All patients on BSC had at least one comorbidity and 84 % of patients on systemic therapies had comorbidities, as detailed in Table 1. The median percentage of blasts in bone marrow prior to initiation of treatment was 29.3 % in the systemic therapy group and 52 % in patients on BSC.

The most common first-line treatment was 5-azacytidine, which was administered to 34 patients (54.8 %), while decitabine was administered as first line in 23 (37.1 %), BSC included hydroxyurea and transfusion support, as per general practice. Median time from diagnosis to initiation of any treatment (either systemic or BSC) was 13 days (interquartile range [IQR] 5.0–27.0). In the systemic treatment group, a median of 10 cycles were received (IQR 2–17). An antibiotic was given as prophylaxis at first-line therapy in 61.4 % of patients receiving systemic treatment and in all patients receiving BSC. Seven patients received second-line treatment (4 decitabine, 1 venetoclax, and 2 other therapy, Supplemental Fig. 1). No patient received an FLT3 inhibitor since these were unavailable at the time of the study.

3.2. Response to treatment

Best overall responses are shown in Fig. 1. Of the 62 patients in the systemic therapy group, 31 (50 %) achieved a response (CR + CRi + PR). CR/CRi was achieved in 33.9 % and median duration of response was 8.2 months; none of the patients receiving BSC achieved CR/CRi/PR and the majority (66.7 %) had stable disease. Median time to best response was 4.5 months for systemic therapy group. MRD was measured with flow cytometry (26.1 % of patients) and RT-PCR (73.9 %). Twenty-three patients on systemic therapy were analyzed for MRD and of these 4 (17 %) had undetectable MRD: MRD was undetectable in 1/15 patients (5.9 %) analyzed by real-time PCR in peripheral blood; MRD in bone marrow was analyzed in 6 patients by flow cytometry (2 with undetectable MRD) and in 2 patients by real-time PCR (1 with undetectable MRD).

3.3. Survival

OS and PFS according to the type of treatment are shown in Table 2. In the entire cohort receiving first-line systemic therapy, median OS was 13.4 months versus 2.7 in those who received BSC. In particular, median OS reached 15.0 months (95 % CI 11.8, 23.9) in those receiving an HMA as first-line systemic therapy. Median PFS ranged from 2.5 months in the BSC arm to 11.8 months in the HMA arm. Kaplan–Meier curves for OS in subgroups based on response are shown in Fig. 2. Median OS was 22.8 months in patients achieving CR/CRi, 18.5 months in those with PR, and 9.4 months in patients with SD/PD.

3.4. Time-to-treatment failure

Forty-seven patients in first-line systemic therapy (75.8 %) and 11 (91.7 %) in BSC experienced treatment failure.

Median TTF was 9.9 months (95 % CI 5.5, 13.3) in patients receiving HMA and 2.5 months in those receiving BSC (Table 2).

The main reasons for discontinuation were disease progression in those receiving first-line systemic therapy (47.3 %) and death (100 %) in BSC patients.

Table 1
Characteristics of patients and treatment patterns.

	First-line systemic therapy (n = 62)	BSC only (n = 12)
Male	30/62 (48.4 %)	10/12 (83.3 %)
Median age at diagnosis, years (range)	76.5 (58–88)	77.5 (52–89)
Secondary AML	21/62 (33.9 %)	3/12 (25 %)
Type of secondary AML:		
MDS	11 (52.4 %)	3 (100 %)
CMML	1 (4.8 %)	0
MPN	2 (9.5 %)	0
t-AML	7 (33.3 %)	0
Prior HMA for previous disorder:		
Yes	2 (9.5 %)	1 (33.3 %)
No	17 (81 %)	2 (66.7 %)
Unknown	2 (9.5 %)	0
ECOG performance status		
0–1	26/39 (66.7 %)	3/6 (50 %)
≥2	13/39 (33.3 %)	3/12 (50 %)
Unknown	23	6
Molecular profile*		
Any mutation	9/52(17.3 %)	3/11(27.3 %)
TP53	2/9 (22.2 %)	0
RUNX1	1/9 (11.1 %)	0
ASXL1	1/9 (11.1 %)	0
FLT3 (not better specified)	0	1/3 (33.3 %)
FLT3ITD	3/9 (33.3 %)	1/3 (33.3 %)
FLT3TKD	1/9 (11.1 %)	0
CEBPA	1/9 (11.1 %)	0
NPM1	2/9 (22.2 %)	2/3 (66.6 %)
No mutation	43 (69.4 %)	8 (66.7 %)
Unknown molecular profile	10	1
Cytogenetic risk		
Favorable	5/56 (8.9 %)	1/10 (10 %)
Intermediate	27/56 (48.2 %)	6/10 (50 %)
Poor	24/56 (42.9 %)	3/10 (30 %)
Unknown	6	2
First-line treatment received**		
Any comorbity	**52 (84 %)**	**12 (100 %)**
Angina / coronary artery disease	3 (4.8 %)	1 (8.3 %)
Congestive heart failure	1 (1.6 %)	1 (8.3 %)
Arrhythmias	8 (12.9 %)	2 (16.7 %)
Restrictive Lung Disease or COPD	9 (14.5 %)	3 (25.0 %)
Renal failure or CKD stage 3, 4 or 5	0	1 (8.3 %)
Other	47 (75.8 %)	9 (75.0 %)
Unknown	2 (3.2 %)	0
Elevated transaminases (not related to cirrhosis OR renal failure OR CKD stage 3, 4	5 (8.1 %	2 (16.7 %)
Systemic therapy	62 (100 %)	–
HMA (Azacitidine) – monotherapy	34 (54.8 %)	–
HMA (Decitabine) – monotherapy	23 (37.1 %)	–
LDAC	1 (1.6 %)	–
Venetoclax + Azacitidine	1 (1.6 %)	–
Other*	3 (4.8 %)	–
BSC only		12 (100 %)
Prophylactic antibiotic at first-line of treatment	35 (61.4)	9 (100.0)
Hospitalized (yes)	41/62 (66.1 %)	8/12 (66.7 %)
Median number of hospitalizations (range)	2.0 (1–5)	2.0 (1–2)

Abbreviations: BSC, best supportive care; CMML, chronic myelomonocytic leukemia; HMA, hypomethylating agent; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; t-AML, therapy-related acute myeloid leukemia.

* Patients were screened for mutations in the following genes: IDH1, IDH2, TP53, TET2, RUNX1, DNMT3A, ASXL1, K/NRAS, FLT3 (either FLT3-ITD or FLT3TKD), CEBPA, JAK2, NPM1, IKZF2, SRSF2, and MLL (i.e. MLL-PTD).

** Patients could also be treated with a combination of therapies.

3.5. Healthcare resource utilization

Healthcare resource utilization was considered in terms of hospitalizations and transfusions. Data on first hospitalizations are shown in Table 3. Most patients required at least one hospitalization (61.0 % and 62.5 % of systemic and BSC patients, respectively). In those receiving first-line systemic therapy, an additional 19.5 % required a second hospitalization, while 19.5 % required ≥3 hospitalizations. In those receiving BSC, 37.5 % required a second hospitalization, and none required ≥3 hospitalizations (Table 3). The main reason for the first hospitalization of systemic patients was related to infections (45.6 %). Patients undergoing systemic therapy were hospitalized for a mean of 16.9 days vs. 19.9 days for BSC.

Most patients had blood transfusions (85.5 % of systemic patients and 100 % of those receiving BSC) during treatment. Among those receiving systemic therapy and in the BSC group, respectively, a median of 8.5 / 11.5 red blood cells transfusions and of 2 / 9 platelet units were needed.

4. Discussion

The present study provides real-world insights into the clinical and hematologic characteristics, treatment patterns, and outcomes of patients with AML who were deemed unfit to receive intensive chemotherapy in Italy in the years 2015–2018. In AML patients who are unfit for intensive chemotherapy, overall, outcomes are generally poor, although these outcomes are clearly superior in patients undergoing first-line systemic therapy compared to those receiving BSC only. In this cohort of patients, the choice of treatment (BSC vs systemic) seems not to be impacted by the main biological characteristics of the disease or by age, but rather by performance status and presence of comorbidities, which were more prominent in the BSC population. Notably, 16 % of patients in this study received palliative BSC only, including transfusions support and/or hydroxyurea. Among patients managed with treatment aimed at altering the natural course of disease, low-dose cytarabine (LDAC) was only occasionally used, while HMAs (mainly azacytidine) were the most common first-line treatment choice. This is not surprising, since HMAs have represented the unique advancement in the treatment of older AML patients for years considered most effective before the new molecules trials. Of note, in the global study including 1762 patients from which the Italian data are derived, 1310 (74.3 %) received systemic therapies: 809 HMA (45.9 %), 199 LDAC (11.3 %), and 302 other (17.1 %), while 452 (25.7 %) received BSC [7]. Thus, substantially fewer patients in Italy received only BSC compared to the global analysis, as well as systemic therapies defined as “other”. Median OS was 9.9, 7.9, 5.4, and 2.5 months for HMA, LDAC, other, and BSC, respectively, compared to 15.0, 2.4, 14.7, and 2.7 months in the Italian sub-analysis.

Available information on healthcare resources utilization were limited to hospitalizations and transfusion. In the global study, most patients were hospitalized for treatment administration, transfusion, or infection [6]. As expected, in the Italian cohort the need for both hospitalization and transfusions was higher in the BSC group, which included more patients with poor performance status and comorbidities.

The median OS of 15.0 months observed in patients receiving an HMA as first-line systemic therapy seen herein is somewhat higher than other historical cohorts. In the phase 3 trial by Dombret et al., OS in patients receiving azacytidine was 10.4 months [10]. Similarly, in the phase 3 study by Kantarjian et al., median OS was 7.7 months in patients receiving decitabine [11]. Real-world data on azacytidine confirmed that it is effective as front-line treatment in all patients with AML, with OS of around 10.3 months although this analysis was not limited to fit or unfit patients [12].

Of interest, we found similarity with the retrospective, single-center study on 980 AML patients ≥ 70 years by Talati et al., with a median overall survival of 14.4 months for those receiving HMAs [13]. More recently two sub-analyses from the Canadian and Japanese populations

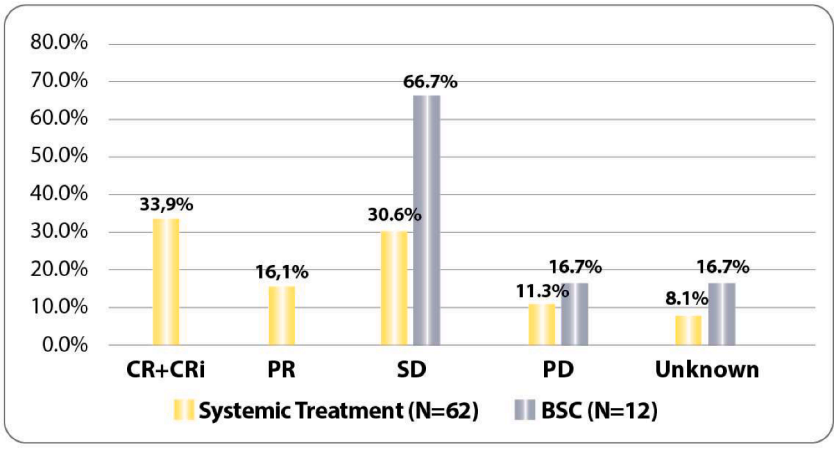

Fig. 1. Best overall responses.
Abbreviations: BSC, best supportive care; CR, complete response; CRi, complete response with incomplete hematological recovery; SD, stable disease; PD, progressive disease.

Table 2
Overall survival and progression free survival.

		Type of first line treatment			
		LDAC ($N = 1$)	HMA ($N = 57$)	Other ($N = 4$)	BSC only ($N = 12$)
OS (months)	Censored - *n* (%)	0	20 (37.7)	0	0
	Deaths - *n* (%)	1 (100)	33 (62.3)	4 (100)	11 (100)
	Median*	**2.37**	**14.96**	**14.65**	**2.70**
	95 % CI of median	NE, NE	11.8, 23.9	2.3, 24.0	2.1, 5.1
	Q1, Q3	2.4, 2.4	9.3, 30.3	5.3, 22.5	2.4, 4.2
PFS (months)	Censored - *n* (%)	0	16 (30.2)	0	0
	Subjects with events - *n* (%)	1 (100)	37 (69.8)	4 (100)	12 (100)
	Median*	**0.23**	**11.84**	**11.31**	**2.48**
	95 % CI of median	NE, NE	7.6, 16,6	2.3, 24.0	1.6, 3.9
	Q1, Q3	0.2, 0.2	5.7, 24.9	5.3, 19.2	1.7, 3.6
TTF§ (months)	Censored - *n* (%)	0	6 (12.5)	0	0
	Treatment failures - *n* (%)	1 (100)	42 (87.5)	4 (100)	11 (100)
	Median Time to Treatment failure *	0.10	9.93	11.62	2.53
	95 % CI of median	NE, NE	5.5, 13.3	1.3, 21.2	1.6, 7.3
	Q1, Q3	0.10, 0.10	3.0, 17.6	2.7, 20.2	1.7, 7.3
	Min, Max	0.10, 0.10	0.13, 41.23	1.35, 21.21	1.55, 8.15

Abbreviations: BSC, best supportive care; HMA, hypomethylating agent; LDAC, low dose cytarabine; TTF, Time to Treatment Failure.
§ Time to Treatment Failure: Time from start of systemic therapy including low-intensity chemotherapy, targeted therapy or BSC until discontinuation of the treatment for any reason including disease progression, death, toxicity, or patient or physician choice.
* Log-rank test p-value < 0.001.

enrolled in CURRENT were published and showed different results in terms of survival among patients treated with HMAs [8,9]. The Canadian analysis found a median survival of 13.31 months similar to that reported in the Italian one; while the Japanese colleagues observed a mOS of 9.2 months, very close to the overall cohort (9.9 months). Differences among all mentioned studies can be attributed to multiple factors that are mostly related to the type of study or to the AML risk composition of groups. First of all, the number of patients enrolled in the present cohort was small; in addition, given the retrospective nature of the study, data collected from medical charts was not complete and high censoring was observed in survival analysis. Moreover, enrolled patients at each center may not be consecutive and consequently a recall bias cannot be excluded. Lastly, it was not possible to follow-up on additional queries that may have arisen due to the data anonymization needed to allow enrollment without signature of informed consent.

It is also important to note that the studies by Dombret et al. and Kantarjian et al. enrolled only patients with poor- or intermediate-risk cytogenetics [10,11], whereas 5 patients (9.8 %) in the systemic treatment arm in our study had favorable cytogenetic risk: while this reflects the real-world nature of our study, it may be another explanation for the better survival we observed. Notably, it's recently emerging how the baseline comorbidity burden could be a powerful predictor of patients' frailty, correlating with increased incidence of adverse events, especially infections, and predicted overall survival [14]. For this reason, we cannot exclude the possibility that data and results cited here, which mostly did not analyze this aspect, may be different from others, conditioning the results in terms of OS.

Seven patients in the systemic arm received second-line treatment, and its effect cannot be isolated when analyzing OS. In line with other experiences, the median OS in patients treated with HMAs was correlated with the response, ranging from 22.8 months in those with CR/CRi to 9.4 months in patients with SD/PD [15]. On the other hand, if we look at the differences in survival within the three datasets published from the CURRENT study, a possible explanation would be the use of other systemic therapies as a therapeutic alternative. In fact, in the Italian and Canadian cohorts, the majority of patients received HMAs and showed very long OS compared to the global population and the historical data [7,8]. In the global cohort, 23 % of patients received other systemic therapies that included, among others, venetoclax, cytarabine, clarubicin, enocitarabine, or combination therapies, while the Italian / Canadian contributed with only 5 %/6 % respectively. Therefore, patients in the global cohort with favorable characteristics at baseline may

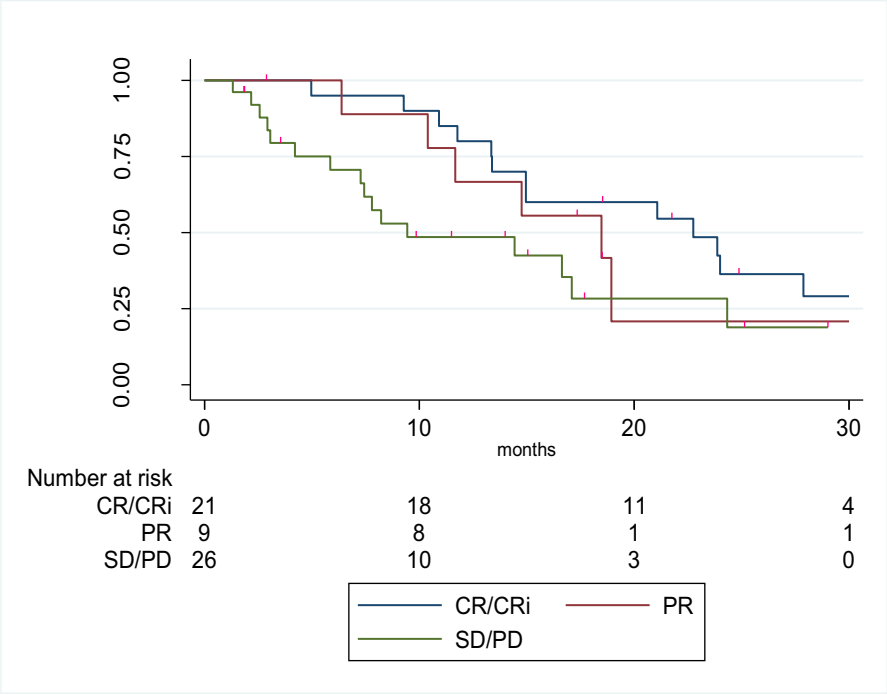

Fig. 2. Kaplan–Meier curves of OS by response.
Abbreviations: CR, complete response; CRi, complete response with incomplete hematological recovery; SD, stable disease; PD, progressive disease; PR, partial response.

Table 3
Healthcare resource utilization: hospitalizations and transfusions.

	First-line systemic therapy ($N = 62$)	BSC ($N = 12$)
Patients hospitalized, *n* (%)	41 (66.1)	8 (66.7)
Hospitalizations, *n*	61	11
No. days hospitalized		
Days, mean (SD)	16.9 (9.8)	19.9 (15.4)
Hospitalizations		
1	61 %	62.5 %
2	19.5 %	37.5 %
≥3	19.5 %	–
Reason for hospitalizations, n (%)		
PD/relapse related	11 (16.2)	1 (9.1)
Infection related	31 (45.6)	1 (9.1)
Transfusion related	1 (1.5)	1 (9.1)
Treatment administration related	15 (22.1)	1 (9.1)
Other AML related event	18 (26.5)	2 (18.2)
Other	12 (17.6)	6 (54.5)
Transfusions, median *N* (IQR)		
Blood	8.5 (4–17)	11.5 (8–16)
Platelets	2 (0–10.5)	9 (3.5–15.5)

Abbreviations: BSC, best supportive care; IQR, Interquartile Range; SD, standard deviation.

have been treated with "other therapies" and frailer or compromised patients were treated with HMAs monotherapy. Finally, the poor survival of the Japanese cohort is justifiable considering the highest median age of that population and the more unfavorable cytogenetic characteristics.

Given the retrospective and real-life nature of the study, data on MRD are scarce and heterogeneous, not allowing us to draw any conclusions.

One of the major limitations of the study is that data were collected through cross-sectional chart review, with a certain amount of missing data. This bias and the limited sample size, confirm an alignment among the three retrospective sub-analyses. The retrospective nature of this study and missing data limit interpretation and deductions as compared to randomized controlled trials.

5. Conclusions

The present analysis provides real-world evidence on treatment patterns and related outcomes in older AML patients in Italy between 2015 and 2018, before the approval of the new target therapies. While confirming the benefits derived from the introduction of HMAs in routine practice, a strong unmet medical need still exists in patients ineligible for intensive chemotherapy. The introduction of novel agents and combinations may impact real-life practice and outcomes in Italy and may enable more patients to achieve a deep and durable remission and a longer survival.

Data availability statement

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (e.g. protocols and Clinical Study Reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications.

This clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

Declaration of competing interest

AbbVie sponsored the study, contributed to the design; participated in data collection, analysis, and interpretation of the data, in writing, reviewing and approval of the publication. No honoraria or payments were made for the publication. Morena Caira, Paola Finsinger and Giuliana Gualberti are AbbVie employees and may own AbbVie stocks and options. Maria Paola Martelli declares honoraria from Rasna Therapeutics, Inc for scientific advisor activities and serves as consultant for scientific advisory boards of Abbvie, Amgen, Celgene, Janssen, Novartis, Pfizer and Jazz Pharmaceuticals. Nicola Di Renzo has nothing to declare. Antonio Curti Abbvie (advisory board, meeting with honoraria), Novartis (advisory board), Jazz (meeting with honoraria), Pfizer (meeting with honoraria). Nicola Stefano Fracchiolla, Luca Maurillo, Felicetto Ferrara, and Attilio Olivieri have nothing to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lrr.2024.100453.

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